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MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
KIM, YUNSOO	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/684,957	**Applicant(s)** WELCHER ET AL.	
	Examiner Yunsoo Kim	**Art Unit** 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *17,18,20,30,31,33,54,55 and 57* is/are withdrawn from consideration.

5)☒ Claim(s) *45-47 and 56* is/are allowed.

6)☒ Claim(s) *1-16,19,21-29,32,34-44,48,49, 51,52 and 58-60* is/are rejected.

7)☒ Claim(s) *50 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *7/21/06*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-60 are pending.

Claims 17, 18, 20, 30, 31, 33, 54, 55 and 57 stand withdrawn from the further consideration by examiner 37 CFR.1.142 (b) as being drawn to a non-elected invention.

Claims 1-16, 19, 21-29, 32, 34-53, 56 and 58-60 are under consideration.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/21/06 has been entered.

3. Applicants' IDS filed on 7/21/06 has been acknowledged.

4. In view of Applicants' response filed 7/21/06, the following rejections remain.

5. Claims 50 and 53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-16, 19, 21-29, 32, 34-44, 48-49, 51-52 and 58-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for both heavy and light chain of anti-IFN- γ antibody comprising all 6 CDRs in proper order and anti-IFN- γ antibody consisting of an entire heavy chain and an entire light chain does not reasonably provide enablement for an anti-IFN- γ antibody light chain, an anti-IFN-γ antibody heavy chain, an anti-IFN- γ antibody comprising less than all 6 CDRs (SEQ

ID NO:s 34, 35, 36, 38, 41 and 43), anti-IFN- γ antibody comprising less than 100% identical (i.e. at least 80%, 90%, 91%, 93%, 96% or 98%) to given antibody SEQ ID NOs: 6, 8, 10, 12, 14, 16-22 and 30-33 (including any changes in CDRs in SEQ ID NO:s 34, 35, 36, 38, 41 and 43 or portion thereof), anti-IFN- γ antibody comprising heavy and light chains of any given SEQ ID NOs: 6, 8, 10, 12, 14, 16-22 and 30-33 and fully human antibody to IFN- γ.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants' arguments filed 7/21/06 have been fully considered but they are not persuasive.

Applicants traversed the rejection based on that the heavy chain variable regions can bind the antigen in absence of light chains and heavy chain CDR3 alone can determine the binding specificity.

The '516 patent teaches that the antigen binding of heavy chain variable regions. However, the claimed invention is drawn to a monoclonal antibody and the specification of the instant application on p. 2 defines that the antibody comprises both heavy and light chains. Thus, the reference teaching is not commensurate with the scope of the claimed invention.

In addition, as taught by Chen et al. (J. Exp. Med. 1992, vol. 176, p. 855-866, newly cited, abstract and discussion, in particular), CDR2 sequence is necessary in binding of an antigen. A single substitution in CDR2 region lead lost in binding activity to the antigen. Claims 1-3 and 21 as recited encompass any isolated antibody comprising a portion (note "at least" language) of CDR3 and any undisclosed sequences of CDRs 1-2. Therefore, claims as drafted do not maintain antigen binding of the claimed antibody.

Furthermore, claims 1, 21, 29, 37 and 40 recite "at least 5 (or 6 or 8) of amino acids in ...in the same order and spacing as they occur in SEQ ID NO:XX (CDR 3sequences)". The specification does not define the phrase to be "consecutive amino acid" but rather any random number of amino acids as long as they appear at the relative positions (see p. 17-18 overlapping paragraph). This allows any 3 mutations in SEQ ID NO:36 consisting of 8 amino acids as drafted in claim 40, for example. This means to encompass any antibodies comprising mutations at positions 2, 4 and 6th of SEQ ID NO:36 and the structure of conformation of the CDR3 are not maintained. Given that an epitope comprises 6-12 amino acids, the claimed CDR3 will not bind to a given antigen.

Moreover, claim 4 for example as recited encompasses any antibody with at least 50 amino acid sequences of SEQ ID NO:10, 14 or 30 out of 117 amino acids. Claim 58 recite "a fragment... fragment comprises at least 20 amino acids". These limitations include any antibodies comprising a fragment of 20 amino acids (or 50) from recited SEQ ID NO:s with any undisclosed amino acids of any length. The instant application does not provide any guidance that amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin.

Claims 9 and 15 are included in this rejection because the matching first amino acid sequences are 90% identical to SEQ ID NOs: 6, 10, 14, 17, 19, 21, 30 and 32.

The art acknowledges that function cannot be predicted based solely on structural similarity to a protein and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Attwood (Science 2000; 290:471-473, newly cited) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39, newly cited) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531, newly cited) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

In addition, the instant application does not show any working example demonstrating a heavy chain variable region alone which exhibits antigen binding.

To summarize, reasonable correlation must exist between the scope or the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breath of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 1-16, 19, 21-29, 32, 34-40, 48-49, 51-52 and 58-60 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the office action mailed 9/26/05 and maintained in the office action mailed 4/17/06.

Applicants' arguments and the references filed on 7/21/06 have been fully considered but they are not persuasive.

Applicants traversed the rejection based on that the sequence identity as recited with representative description is sufficient to satisfy the written description elements.

The phrase "at least 90% sequence identity to SEQ ID NO:32" as in claim 11 includes 1.16×10^{33} different amino acid combinations. Claims as drafted are not limited to include variants with known structural and functional property as Applicants assert but encompass any isolated antibody of 50 amino acid sequences of SEQ ID NOs:6, 10 or 14 or fragment of 20 amino acids.

Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 41 and 43 stand rejected under 35 U.S.C. 102(b) as being anticipated by Thakur et al. (Molecular Immunology, 1999, vol. 36:1107-1115, IDS reference, of record) for the reasons set forth in the office action mailed 9/26/05 and maintained in the office action mailed 4/17/06.

Applicants' arguments and the references filed on 7/21/06 have been fully considered but they are not persuasive.

Applicants traversed the rejection based on that the reference teaches changing 65 and 103 residues of rhesus IFN- γ to human IFN- γ residues is required for AF2 binding activity. Applicant further argues that Thaker does not teach changing 19 and 20 residues of human IFN- γ to rhesus IFN- γ residues.

Thakur et al. teaches murine monoclonal antibody (AF2) which inhibits biological activity of human IFN- γ (i.e. neutralizing activity, prevent IFN- γ from binding to cell surface) and chimpanzee (abstract, e.g. AF2 neutralize IFN- γ from higher primates) and does not inhibit cynomologus monkey (Applicants acknowledges in remark p. 23 the amino acid sequences of cynomologus monkey and rhesus IFN- γ are identical) (abstract, p. 1111, right col. last paragraph, in particular). AF2 recognizes and inhibits human and chimpanzee IFN- γ and AF2 does not bind and inhibit rhesus IFN- γ. Thakur discloses various IFN- γ sequences of primates in Table 1 (p.1112, in particular) and lists Histidine at 19, Serine at 20, Serine 65 are derived from human as well as other differences between human and rhesus. The limitation of claim 41 is an isolated antibody that can inhibit human and chimpanzee IFN- γ but cannot inhibit rhesus IFN- γ. The antibody that cannot inhibit rhesus IFN- γ will have the rhesus derived IFN- γ at amino acids 19 and 20. As shown in Thakur reference, AF2 does not bind and inhibit rhesus IFN- γ having aspartate at 19 and proline at 20 (Table 1, in particular). Table 2 shows that the IFN- γ construct having rhesus (1-29) sequence was not induced by AF2. The only sequence differences between the human and rhesus between 1-20 arise at positions 19 and 20 and the Table explicitly teach that the rhesus amino acid sequence at 19 and 20 are required. Thus, prior art teachings anticipate the claimed invention.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 41-44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thakur et al. (Molecular Immunology, 1999, vol. 36:1107-1115, of record) in view of U.S.Pat. No. 6,075,181 (of record) for the reasons set forth in the office action mailed 9/26/05 and maintained in the office action mailed 4/17/06.

Applicants' arguments and the references filed on 7/21/06 have been fully considered but they are not persuasive.

Applicants traversed the rejection based on that the Thakur reference is not anticipatory thus it is not obvious to combine the teachings.

The teachings of Thakur et al. have been discussed, supra.

Thakur et al. does not teach human or humanized antibody.

However, the '181 patent teaches fully human antibodies (Examples 1-6) generated by immunizing xenomice with immunogens (i.e. IFN- γ, col. 8-9, abstract) and the fully human antibodies generated by the xenomice methods are highly specific for human and desirable for therapeutic use (col. 1, lines 48-63).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make human/humanized antibody as taught by the '181 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because fully human antibodies as taught by the '181 patent to develop less immunogenic but immunospecific human antibodies for therapeutic and diagnostic uses.

From the teachings of the references, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of the ordinary in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of discussion above, it is the examiner's position that the combination of teachings remains obvious.

13. The following new grounds of rejections are necessitated by Applicants' amendments and addition of new claims filed on 1/30/06.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 43-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

Claims 43-44 currently claim "mutations **consist** of the following" and the specification or the original claim provide support for the mutation is limited to that particular positions and Applicants fail to provide where the support comes from.

16. Claims 45-47 and 56 are allowable.

SEQ ID NO:s 6, 8, 10, 12, 14, 16-22, 36, 37, 43 and 44 are free of art.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yunsoo Kim whose telephone number is 571-272-3176. The examiner can normally be reached on Monday thru Friday 8:30 - 5:00PM.If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yunsoo Kim
Patent Examiner
Technology Center 1600
September 22, 2006

Christina Chan
CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600